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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/857,783	11/13/2001	Itamar Willner	10980-16001	8069
20985	7590	11/18/2005	EXAMINER	
FISH & RICHARDSON, PC			LU, FRANK WEI MIN	
P.O. BOX 1022			ART UNIT	
MINNEAPOLIS, MN 55440-1022			PAPER NUMBER	

1634

DATE MAILED: 11/18/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/857,783	Applicant(s) WILLNER ET AL.	
	Examiner Frank W Lu	Art Unit 1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 09 September 2005.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☐ Claim(s) 1-8 and 23-33 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☒ Claim(s) 23-25 is/are allowed.
- 6) ☒ Claim(s) 1-3 and 26-33 is/are rejected.
- 7) ☒ Claim(s) 4-8 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 06 June 2001 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

CONTINUED EXAMINATION UNDER 37 CFR 1.114 AFTER FINAL REJECTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission of RCE and the amendment filed on September 9, 2005 have been entered. The claims pending in this application are claims 1-8 and 23-33. Rejection and/or objection not reiterated from the previous office action are hereby withdrawn in view of amendment filed on September 9, 2005.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 26-33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

4. Claim 26 is rejected as vague and indefinite because it is unclear what means "said sensor device comprises a quartz-crystal microbalance". Does "quartz-crystal microbalance" mean "quartz-crystal microbalance probe"? Please clarify.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

6. Claims 1 and 2 are rejected under 35 U.S.C. 102(e) as being anticipated by Blackburn *et al.*, (US Patent No.6,686,150, priority date: January 29, 1998).

Blackburn *et al.*, teach a method for detecting a target sequence in a sample comprising:

a) providing a rolling circle probe (RCP) comprising: i) a first ligation sequence substantially complementary to a first domain of said target sequence; ii) a second ligation sequence substantially complementary to a second domain of said target sequence; and iii) a priming sequence; b) hybridizing said first ligation sequence to said first domain and said second ligation sequence to said second domain to form a first hybridization complex; c) ligating said first and second ligation sequences together; d) adding to said first hybridization complex: i) a primer substantially complementary to said priming sequence; ii) a polymerase; iii) dNTPs; and iv) an electron transfer moiety (ETM); to form a rolling circle concatamer comprising at least one covalently attached ETM; and e) detecting said ETM as an indicator of the presence of said target sequence wherein said RCP further comprises a third domain comprising a capture sequence, and said method further comprises hybridizing said concatamer to a capture probe covalently attached to an electrode (see columns 141, claims 1 and 2).

Regarding claim 1, since Blackburn *et al.*, teach to make a rolling circle concatamer by hybridizing a RCP comprising a first ligation sequence and a capture sequence to a target sequence and the ligation and amplification reactions and hybridize said concatamer to a capture probe covalently attached to an electrode (see columns 141, claims 1 and 2), Blackburn *et al.*, disclose a sensor device (ie., an electrode) having a sensing interface carrying capturing oligonucleotides wherein each carrying capturing oligonucleotide has a nucleotide sequence (ie., multiple identical capture probes), a stably hybridizing portion of which is complementary to a first portion (ie., a capture sequence) of the target oligonucleotides (ie., RCP in said concatamer having RCP wherein RCP is the target oligonucleotide here) wherein said sensor device comprises an electrochemical probe carrying the sensing interface (ie., an electrode) and the probe is located in a surrounding medium (ie., the hybridization buffer) as recited in (a) of claim 1, providing verification oligonucleotides wherein each verification oligonucleotide has a nucleotide sequence (ie., multiple identical target nucleic acids), a stably hybridizing portion of which is complementary to a second portion of the target oligonucleotide (ie., a first ligation sequence of RCP), other than said first portion as recited in (b) of claim 1, contacting the sample (ie., said concatamer having RCP) with the sensing interface under conditions such as to allow the target oligonucleotides (ie., RCP in said concatamer) if present in the sample, to hybridize to the capturing oligonucleotides (ie., multiple identical capture probes on the electrode) as recited in (c) of claim 1, and prior to (c), allowing the verification oligonucleotides (ie., multiple identical target sequences) to hybridize to the target oligonucleotides (ie., RCP) if present in the sample as recited in (d) of claim 1. Since Blackburn *et al.*, teach detecting said ETM as an indicator of the presence of said target sequence (see column 141, claim 1) and insulators (such

Art Unit: 1634

as resistance) is used to monitor electron transfer between ETM and the electrode (see column 92, fourth paragraph), and the measurement of insulators (such as resistance) must be performed in or through the hybridization buffer (ie., having ETM), Blackburn *et al.*, disclose detecting the presence of said verification oligonucleotides (ie., the target sequence) on the sensing interface by measuring insulation of the sensing interface (ie., surface of the electrode) to interfacial electron transfer between the sensing interface and the surrounding medium (ie., the hybridization buffer containing ETM) as recited in (e) of claim 1.

Regarding claim 2, Blackburn *et al.*, teach that said detection is based on Faradaic impedance spectroscopy or amperometric measurements (see column 91, last paragraph and columns 92 and 96).

Therefore, Blackburn *et al.*, teach all limitations recited in claims 1 and 2.

Response to Arguments

In page 7, fourth paragraph bridging to page 10, third paragraph of applicant's remarks, applicant argues "the methods of Blackburn employ an oligonucleotide that has bound to it, e.g., via a covalent bond, to a electron transfer moiety (ETM) such as ferrocene. This is shown below in a portion of Fig. 30 from Blackburn. The oligonucleotide is detected by measuring electron transfer between the ETM, which is bound to an oligonucleotide, and the electrode - not between the surrounding medium and the electrode as suggested by the examiner. Detection of the oligonucleotide occurs because the ETM is brought into proximity to the electrode".

This argument has been fully considered but it is not persuasive toward the withdrawal of the rejection. First, as shown in above rejection and claims 1 and 2, since Blackburn *et al.*, teach that concatamer comprising at least one covalently attached ETM is attached to an electrode by

Art Unit: 1634

hybridizing to a capture probe which is covalently attached to the electrode, the complex formed by the electrode, the concatamer and the capture probe is a complex formed by the sensing interface, the capture oligonucleotide, target oligonucleotide, and verification oligonucleotide (see top of page 9 of applicant's remarks). Since Blackburn *et al.*, teach detecting said ETM as an indicator of the presence of said target sequence (see column 141, claim 1) and insulators (such as resistance) is used to monitor electron transfer between ETM and the electrode (see column 92, fourth paragraph), and the measurement of insulators (such as resistance) must be performed in or through the hybridization buffer (ie., having ETM), Blackburn *et al.*, disclose detecting the presence of said verification oligonucleotides (ie., the target sequence) on the sensing interface by measuring insulation of the sensing interface (ie., surface of the electrode) to interfacial electron transfer between the sensing interface and the surrounding medium (ie., the hybridization buffer containing ETM) as recited in (e) of claim 1. Second, the rejection is not based on Figure 30 of US Patent No.6,686,150.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any

Art Unit: 1634

evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claim 3 is rejected under 35 U.S.C. 103(a) as being unpatentable over Blackburn *et al.*, (January 29, 1998) as applied to claims 1 and 2 above, and further in view of Lizardi *et al.*, (US Patent NO. 6,143, 495, filed on November 21, 1996).

The teachings of Blackburn *et al.*, have been summarized previously, *supra*. Blackburn *et al.*, teach that the size of RCP is designed such that it hybridizes “smoothly” to many capture probes on a surface (see column 25, lines 33-37).

Blackburn *et al.*, do not disclose that the stably hybridizing portions of the capturing and verification oligonucleotides are of about 12 nucleotides as recited in claim 3.

Lizardi *et al.*, teach that a region in a detection tag with 10-35 nucleotides forms a specific and stable hybridization complex with a detection probe (see column 10, second paragraph).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed the method recited in claim 3 wherein the stably hybridizing portions of the capturing and verification oligonucleotides are of about 12 nucleotides in view of patents of Blackburn *et al.*, and Lizardi *et al.* One having ordinary skill in the art has been motivated to do so because optimization of sizes of the stably hybridizing portions of the capturing and verification oligonucleotides, in the absence of convincing evidence to the contrary, would have been obvious to one having ordinary skill in the art at the

Art Unit: 1634

time the invention was made. One having ordinary skill in the art at the time the invention was made would have been a reasonable expectation of success to design the capturing and verification oligonucleotides wherein their stably hybridizing portions are about 12 nucleotides so that they hybridize “smoothly” to their corresponding capture probes on a surface and specific and stable hybridization complexes would be formed. More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation. Where the general conditions of a claim are disclosed in the prior art, it is not inventive, in the absence of an unexpected result, to discover the optimum or workable ranges by routine experimentation. *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955) (MPEP 2144.05).

Response to Arguments

In page 11, fourth paragraph of applicant’s remarks, applicant argues that “Blackburn does not disclose a method that includes ‘measuring insulation of the sensing interface to interfacial electron transfer between the sensing interface and the surrounding medium’ as required by claims 1 and 3. Lizardi et al. does not suggest such a method. Thus, Blackburn and Lizardi et al., no matter how combined, cannot render claim 3 obvious”.

This argument has been fully considered but it is not persuasive toward the withdrawal of the rejection because Blackburn do teach a method that includes “measuring insulation of the sensing interface to interfacial electron transfer between the sensing interface and the surrounding medium” as required by claim 1 (see above Response to Arguments to the rejection under 35 USC 102).

Art Unit: 1634

Conclusion

9. Claims 4-8 and 26-33 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

10. Claims 23-25 are allowed over prior art.

11. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CAR § 1.6(d)). The CM Fax Center number is (571)273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frank Lu, Ph.D., whose telephone number is (571)272-0746.

The examiner can normally be reached on Monday-Friday from 9 A.M. to 5 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (571)272-0745.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.



Frank Lu
Primary Examiner
November 10, 2005